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Geomagnetic activity and enhanced mortality in rats with acute (epileptic) limbic lability

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Abstract. Presumably unrelated behaviors (e.g. psychiatric admissions, seizures, heart failures) have been correlated with increased global geomagnetic activity. We have suggested that all of these behaviors share a common source of variance. They are evoked by transient, dopamine-mediated paroxysmal electrical patterns that are generated within the amygdala and the hippocampus of the temporal lobes. Both the probability and the propagation of these discharges to distal brain regions are facilitated when nocturnal melatonin levels are suppressed by increased geomagnetic activity. In support of this hypothesis, the present study demonstrated a significant correlation of Pearson $r=0.60$ between mortality during the critical 4-day period that followed induction of limbic seizures in rats and the ambient geomagnetic activity during the 3 to 4 days that preceded death; the risk increased when the 24 h geomagnetic indices exceeded 20 nT for more than 1 to 2 days.

Key words: Geomagnetic activity – Death – Rat – Limbic – Epilepsy

Increases in geomagnetic activity have been associated with a diffuse array of organismic changes that include increased psychiatric admissions (Friedman et al. 1963; Traute and Duell 1935), bereavement hallucinations (Persinger 1988), visual hallucinations (Randall and Randall 1991), alterations in nocturnal nociception (Kavaliers and Ossenkopp 1988), reduced convulsive thresholds (Keshavan et al. 1981; Rajaram and Mitra 1981) and general indicators of circadian desynchronization (Persinger 1980). Most of these symptoms occur during the night, although the overt sequelae (e.g. psychiatric referral) may not occur until the next day.

Convergent interpretation of the research suggests that a central neurophysiological process evokes this wide domain of behaviors. Strong inferencing from the results that have been collected in this laboratory over the last decade suggests that the actual neuromechanism involves: (i) electrical lability within the amygdala and hippocampus of the temporal lobes and (ii) the enhancement of this lability by geomagnetic activity-induced suppression of nocturnal melatonin levels. We have hypothesized (Persinger 1983, 1988) that disruption in the nocturnal patterns of pineal melatonin activity facilitates the electrical lability of deep subcortical temporal lobe structures. Although no one has reported longitudinal measures of both geomagnetic activity and nocturnal melatonin levels, cross-sectional analyses have implied the association.

There is a strong relationship between paroxysmal electrical activity within the deep structures of the temporal lobes and the symptoms that are generally given psychiatric classifications (Gloor et al. 1982). Schizophreniform and affective disorders are frequently associated with electrical lability within the temporal lobes in abnormal populations (Seidman 1983). However, less extreme equivalents of these behaviors exist for briefer periods within the normal population (Persinger 1991). Persinger and Makarec (1987) have shown a continuum of temporal lobe lability along which all people are distributed. Normal people who show signs and symptoms of temporal lobe activity, such as psi experiences, a sense of meaningfulness, mystical sensations and depersonalization, may also be more sensitive to extremely low-frequency magnetic fields within the microT and even the nanoT range (Persinger et al. 1992b; Ruttan et al. 1990; Subrahmanyam et al. 1985).

Mammals, including human beings, appear to display normal periods of nocturnal microseizure activity that originate within the amygdala and hippocampus; these paroxysmal periods are important for the pulsatile release of hypophyseal hormones. Most of these paroxysmal discharges occur during the normal nightly phasic periods of dreaming or rapid eye movement (REM) sleep (Stevens 1982), when melatonin levels are briefly lower than during non-REM sleep (Foley et al. 1986). During REM, transient periods of disruption in homeostasis

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(such as cardiac aperiodicity and tachycardia) occur in vulnerable subpopulations. Commensurate with this pattern is the observation that epileptoid activity emerges in rats following pinealectomy (Anton-Tay 1971) and that introduction of melatonin lowers the excitability of pyramidal and granule neurons within the hippocampal formation (Zeise and Semm 1985).

Suppression of nocturnal levels of circulating melatonin (Wilson et al. 1990) or its synthesizing enzyme within the pineal gland (Welker et al. 1983) by alterations in the parameters of magnetic fields has been reported (Semm 1988); the mechanism may involve Ca^{++} cyclotron resonance (Lerchl et al. 1991). Brief (<1 h) exposure to weak, extremely low-frequency (0.5 to 60 Hz) magnetic fields or changes in the direction of the earth's static magnetic field suppress nocturnal melatonin levels to less than one-third of the normal value (Olcese and Reuss 1986); the reversibility of the effect, the same night, depended upon when the stimulus had been applied during the scotophase.

Suppression of melatonin by increases in geomagnetic activity has been inferred by lowered convulsive thresholds and by alterations in behaviors that are associated with melatonin synthesis. However the Ossenkopp and Kavaliers team (Kavaliers and Ossenkopp 1988; Ossenkopp et al. 1983) has shown that the changes in nocturnal nociceptive thresholds occurring within 30 min of exposure to experimental magnetic fields within the microT range were also observed during an intense (daily aa >50 nT) geomagnetic storm that lasted for several days. In at least one study (Bardsano et al. 1989), quantitative changes in the synaptic ultrastructure of pinealocytes at the time of sacrifice appeared to reflect the magnitude of the ambient geomagnetic activity.

Our general hypothesis is that all terrestrial organisms are sensitive to increases in geomagnetic activity above a specific threshold (Persinger et al. 1973) and that the effects in higher animals are mediated through disruption of the nocturnal peak in melatonin periodicity and the subsequent activation of the amygdala and hippocampus (Persinger 1988). Any condition that enhances the electrical lability of these deep temporal lobe structures also increases their sensitivity to this global environmental stimulus. Limbic epilepsy is one form of extreme electrical lability that primarily involves temporal lobe structures.

Experimental limbic epilepsy in rats can be induced with a single systemic injection of lithium (3 mEq/kg) followed 4 to 24 h later by 30 mg/kg of the muscarinic agent pilocarpine (Honchar et al. 1983). Unless 30 mg/kg of acepromazine is given within 30 min after the onset of the seizures, the rats develop status epilepticus and die within about 24 h (Persinger et al. 1988); the mortality is always two to four times more frequent in males than in females. Continuous monitoring suggests that death is associated with sudden cessation of cardiac function (preceded by an hour or more of aperiodicity) rather than with a slow decline in activity (Persinger and Harrigan, in preparation).

Until recently, the mortality rate within 4 days was less than 20% if acepromazine had been given. Within the last 2 years, the mortality has slowly increased at times to 50%; the source of this problem has not been clear. However during the large geomagnetic storm of 5 June, 1991, an inordinate number of treated rats died. On the bases of these results and the coincident death of epileptic patients within the region, the mortality records were carefully examined as a function of concomitant geomagnetic activity.

Materials and methods

Between June 1989 and January 1991, a total of 194 male Wistar albino rats were involved in a total of 15 experiments; there were approximately 6 to 9 rats per experiment. The rats were between 80 and 120 days of age. Throughout the experiments the rats were maintained in standard caging within a climate controlled room (20–22° C); the light/dark (LD) cycle was 12:12 h with the local daylight cycle beginning at 0800 hours.

As a part of a routine protocol, each rat had been injected subcutaneously with 3 mEq/kg of lithium chloride (3 mEq/ml); 4 h later (approximately 1400–1600 hours) each rat had been injected subcutaneously with 30 mg/kg of pilocarpine and then placed in an observation box. Limbic motor seizures, as defined by the gradual evolution of facial automatisms into forepaw clonus, rearing and falling (which preceded status epilepticus), were observed in all rats. All seizures were evident between 20 and 40 min after the injection of the pilocarpine.

The acepromazine was administered (s.c.; 30 mg/kg) 60 min after the injection of the pilocarpine; the rat was then returned to its home cage. Effects of the tranquillizer, always verified by visual inspection, were evident within 30 min. Mortality was recorded daily. For the present study all rats that died within 4 days (see Fig. 1) after the onset of the seizures were included. This criterion was used because the period constitutes the inflection point in the cumulative mortality curve and rats who die after this period often show other confounding contributions.

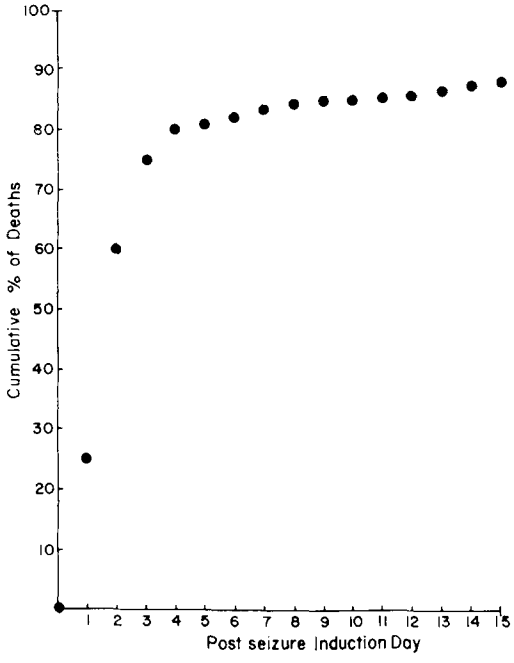

Fig. 1. Cumulative percentage of deaths as a function of time from the induction of status epilepticus by systemic lithium/pilocarpine and treatment by acepromazine

Table 1. Partial correlation coefficients (r) after removal of shared day-time variance, between nocturnal activity and global geomagnetic activity between December 1989 and May 1990

Rat number	Lag (of geomagnetic days)							
	0	−1	−2	−3	−4	−5	−6	−7
1	−0.11	−0.17*	−0.22*	−0.20*	−0.18*	−0.11	−0.10	0.02
2	−0.14	−0.19*	−0.22*	−0.18*	−0.11	−0.05	0.01	0.06
3	−0.15	−0.23*	−0.27**	−0.27**	−0.13	−0.04	−0.16	−0.01
4	−0.17*	−0.16	−0.15	−0.17*	−0.07	0.00	−0.02	0.02

*$P<0.05$; **$P<0.001$

A total of 102 rats met this criterion. The percentage mortality for the total number of rats in which seizures had been induced were determined for each experiment. The daily aa values for the northern hemisphere (Mayaud 1973) were obtained from the Monthly Geomagnetic Summary for each of the 3 days before, the day of and for each of the 3 days after the seizure induction. Daily aa values for each of the 4 days before, the day of and for each of the 4 days after each rat's death were also determined. Because multiple deaths occurred on some days, a separate file involving the same geomagnetic data was determined for death days only. For the analysis of percentage mortality, Pearson correlations were completed; for the first two analyses, repeated measures analyses [multivariate analysis of variance (MANOVA; SPSSX)] were completed for the daily aa values.

Between December 1989 and May 1990, the ambulatory activity of 4 rats was monitored continuously. Each rat was maintained within a $27 \times 27 \times 45$ cm clear plastic cage. Food and water were available within the cage; the corncob bedding was changed every 7 to 10 days. Two sets of infra-red photocells were placed along the long axes of each cage. The total number of interruptions of the beams per 10 min was determined for each cage by a microcomputer. These data were then loaded onto a VAX computer system; the mean numbers of counts for the 72 10-min increments of the light cycle and for the 72 10-min increments of the dark cycle were calculated automatically for each 24 h period.

For each day during the observation period, each rat's nocturnal and light activity as well as the 24-h aa value (northern hemisphere) were obtained. Lag values for the aa measures during the 1 to 7 days before the activity were calculated by computer software. In order to remove the contribution of laboratory and cultural noise (e.g. changing bedding), the shared variance between light and dark cycle activity was removed before lag analyses were completed between the latter and geomagnetic activity. All analyses involved SPSSX software on a VAX 4000 computer.

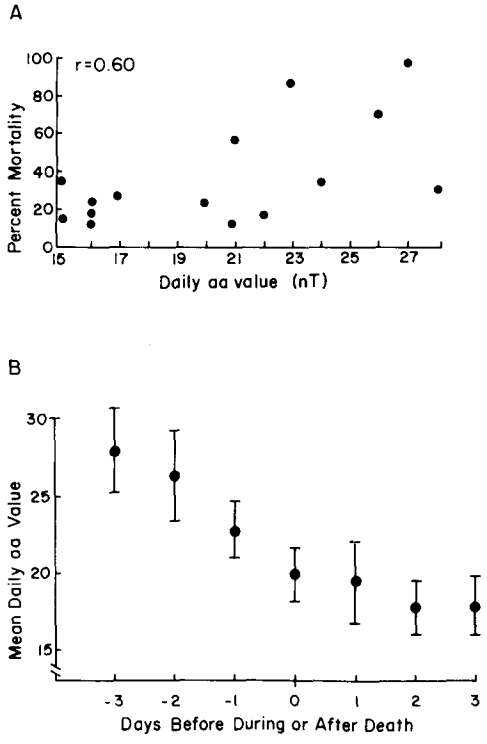

Fig. 2. **A** Scattergram of the correlation between percentage mortality of rats in which seizures had been induced and the daily geomagnetic activity (aa value) during the second day after the induction. **B** Mean daily aa values for days before, of and after the deaths of rats in which seizures had been induced

Results

Mortality

The only statistically significant (Pearson $r=0.60$, $P<0.01$) correlation between percentage mortality and geomagnetic activity occurred 2 days after the induction of the seizures (in the middle of the 4 day mortality period). Figure 2A shows the scattergram. Visual inspection suggests that the increase in mortality over the usual expectation of 20% occurred when the daily geomagnetic aa values exceeded 20 nT.

The mean daily aa values during the days of sudden death and during the days before and the days after the deaths of rats in which seizures had been induced are shown in Fig. 2B. Repeated measure analyses of variance demonstrated a significant difference between days; the conservative Greenhouse-Geiser criterion was also significant. The effect was still significant [$F(6,156)=3.25$, $P=0.005$; Greenhouse-Geiser (3.37, 156), $P=0.02$] when only the death days ($n=27$; controlling for multiple deaths) were analysed. Correlated t-tests indicated that the major source of the daily differences in aa values was due to the increased geomagnetic activity during the days that preceded the sudden death.

Activity study with normal rats

Table 1 shows the strength of the association between nocturnal activity (after the shared variance with daytime activity had been removed by partial correlation analyses) and the daily geomagnetic activity. All four rats showed significant ($P<0.05$) suppressions of nocturnal activity after an increase in geomagnetic activity during the previous 0 to 3 days. To insure that the four rats were not interdependent, the total data (10-min bins) were obtained for five different days (random selec-

tion). There were no significant intercorrelations ($P > 0.05$) between the rats ultraradian cycles.

Discussion

These results confirm our anecdotal observations that increases in 24-h global geomagnetic activity are followed by enhanced mortality in rats in which limbic seizures have been induced. Most of these deaths occurred within 4 days of the single injection of lithium and pilocarpine, during which time there was excessive electrical activity within the limbic (pyriform and entorhinal) cortices and the subcortical (amygdala and hippocampal) structures (Persinger et al. 1992a). These paroxysmal changes have been observed by other researchers (Ormandy et al. 1989) and can be inferred in our studies by the severe and immediate (within 2 days) neuronal necrosis that occurs within these regions.

One primary correlate of death during this sensitive post-seizure period has been sudden cardiac cessation (Persinger and Harrigan, in preparation); it is often preceded, for at least an hour, by increased variability (arrhythmia) in mean heart rate and by premature ventricular contractions (PVC). Rats that received acepromazine, a compound that normally reduces the mortality from more than 95% to less than 20%, displayed a stable normal heart rate. This pattern is commensurate with the conclusion that acepromazine prevents the phasic discharges from the extremely excited limbic structures into the hypothalamic vasomotor centres, thus reducing the risk of sudden death.

As noted in Fig. 2 enhanced geomagnetic activity during the critical 4 days following the seizure induction reduces the efficacy of acepromazine as defined by the proportional increase in mortality. We suspect that the usual prophylactic effect of this phenothiazine derivative is mediated primarily by its antidopaminergic action rather than by its anticholinergic properties. The latter is suggested by the relative (central) hypothermia that occurs during the 12 h following the acepromazine injection for rats in which the lithium-pilocarpine seizures have been induced (McDonald 1991).

If this mechanism is valid, then the enhanced geomagnetic activity may be facilitating the dopamine effects within the amygdaloid-hippocampal complex and entorhinal-pyriform cortices; they are clearly associated with the initiation of the limbic seizure and the latter even promotes kindling (McIntyre and Plant 1989). Because antagonists for dopamine D1 receptors but not D2 receptors prevent the convulsive activity of lithium-pilocarpine treatments (Barone et al. 1991), specific vulnerability within groups of neurons that express this subclass of receptors is indicated.

The resulting stimulation, especially within the amygdala, would enhance the risk of simultaneous paroxysmal volleys directly to the parabrachial-solitary-dorsal vagal nuclei and to the hypothalamic centres that modulate cardiovascular responses. Spencer et al. (1989) found that L-glutamate stimulation of the lateral hypothalamic area evoked bradycardia and reduced blood pressure. The lateral hypothalamic area also projects to the parabrachial nucleus, nucleus of the solitary tract, vagal preganglionic nuclei and the intermediolateral (sympathetic) cell column. If these first two areas are already stimulated, as might be inferred from the pattern of subsequent destruction within their rostral components of the insular cortices (Persinger et al. 1992a), then the effects of the amygdaloid-mediated discharge could produce an intense parasympathetic effect and, subsequently, cardiac block. The prodromes of the sudden death would have the same temporal characteristics that have been verified by cardiac monitoring (Persinger and Harrigan, in preparation).

There is now experimental evidence that prolonged electrical stimulation of the posterior insular cortices (near the rhinal fissure) can induce arrhythmia and sudden death. Oppenheimer et al. (1991) found that insular stimulation triggered by the R wave of the ECG evoked arrhythmia and sudden death within 2 to 8 h; about 50% of the hearts were asystole rather than in fibrillation. The optimal trigger stimulus was about 45 Hz, which is within the range of the typical burst firing pattern of amygdaloid neurons and is a common modal discharge frequency of the amygdaloid complex.

The posterior insular cortices, particularly within the region of the rhinal fissure, receives input from the basolateral amygdala which contains one of the most concentrated cholinergic pools (De Olmos et al. 1985) within the telencephalon. Excessive stimulation of muscarinic receptors by the prolonged lithium/pilocarpine-induced seizure process would be expected to increase afferent stimulation to the chronotrophic cardiac centre within the insula. We postulate that these continuous direct discharges to the parasolitary nucleus and to the amygdala (axons from which also innervate the same portion of the parasolitary nucleus that receives insular efferents), would increase the risk of cardiac arrhythmia and sudden death.

It is documented that the insular cortex sends input to the amygdala, especially the central nucleus (Carpenter and Sutton 1983); the primary transmitter is dopamine. Release of dopamine is a common correlate of elevated gamma-aminobutyric acid (GABA) or GABA mimetics within the brain (Ahtee and Vahala 1985); not surprisingly, elevation of GABA is one of the strongest neurotransmitter changes during the mid-status phase of the lithium-pilocarpine seizures (Walton et al. 1990). Both the GABA-mediated and melatonin-suppression-evoked increase in dopamine would be expected preferentially to trigger the D1 receptors and to reduce the prophylactic effects of acepromazine.

Our working hypothesis that: (i) increases in geomagnetic activity decrease nocturnal melatonin levels and (ii) this decrease encourages the generation of paroxysmal discharges from the amygdaloid-hippocampal complex (resulting in fatal cardiac irritability) does have inferential support. According to Zeise and Semm (1985), melatonin reversibly prevented epileptiform bursts evoked by the GABA-system convulsant bicuculline, when applied to hippocampal slices. In fact these authors also suggested that magnetic fields could reduce the

availability of melatonin within the hippocampus and hence modulate seizure activity.

There is also persistent correlational evidence. Normal rats in the activity experiment exhibited statistically significant negative correlations between night-time activity and the geomagnetic activity of the previous 1 to 3 days only. This quantitative association was present for all four subjects and was very consistent in three of them; the pattern indicated that enhanced geomagnetic activity was associated with a reduction in subsequent nocturnal ambulation.

If we assume that the nocturnal peaks in circulating melatonin levels, the synthesis of melatonin within the pineal organ and ambulatory activity are closely coupled, then it is reasonable to expect that a suppression of the usual peak in nocturnal melatonin would evoke a mild decrease in ambulation. The strength of the correlation, which explained at most 10% of the variance (but even then only after the contribution of spurious disruptions from colony maintenance had been removed), is within the range expected for any average geomagnetic effect. Exposure to experimental magnetic fields within the microTesla range, about 100 times more intense than geomagnetic values or to deviations of the geomagnetic static component angle (about 50 times that of a typical geomagnetic storm), is required in order to reduce melatonin levels by at least 50%.

Another argument that the increased mortality during the post-seizure period was strongly associated with the suppression of melatonin levels (evoked by enhanced 24-h geomagnetic activity) is suggested by this chemical's inhibitory effect upon dopamine release but stimulatory effect upon the pre- and post-synaptic binding of gamma-aminobutyric acid (Rosenstein et al. 1989); suppression of melatonin facilitates dopamine synthesis and release. Considering the copious concentrations of dopamine pathways within the amygdala and the hypothalamus and their shared cardiovascular functions, sudden increases in dopamine could evoke cardiac arrhythmias and sudden death in sensitized organisms.

We think it is relevant that the risk of sudden cardiac death following the induction of Li-pilocarpine seizures is markedly increased when the rats are exposed to continuous light during the subsequent 24 h. Unpublished data by the first author and by T. Harrigan indicate that whereas the immediate initiation of a dark cycle facilitates recovery, exposure to >1000 lux of fluorescent light almost always precipitates sudden cardiac death. Because white light is known to depress melatonin levels and to inactivate its synthesizing enzyme (Foley et al. 1986), these results further support the specific role of an interaction between melatonin-dopamine activity within the limbic system.

Because of the unusually high accumulation of circulating melatonin within the suprachiasmatic nucleus (Vanecek et al. 1989), suppression of melatonin synthesis may directly affect cardiovascular centres within the hypothalamus through its dense intranuclear connections (Rockhold et al. 1990). Melatonin is also known to increase the activity of pyridoxal phosphate, an important coenzyme for the decarboxylase that synthesizes GABA (Dakshinamurti et al. 1988) within the many brain structures. Suppression of melatonin and hence the activity of pyridoxal phosphate and the synthesis of GABA could also release pacemaker neurons from inhibitor control.

Similar processes should occur within the human brain. Its size and multiple "gateway" nuclei attenuate the spread of paroxysmal discharges into clinical convulsions; consequently, transient melatonin suppression would not necessarily be fatal to vegetative function. Instead, the paroxysmal discharges would be spatially contained and would be evident only by the quantitative documentation of complex, partial seizure-like symptoms (Roberts et al. 1990). Microseizure activity within the amygdala and hippocampus has been suspected as a common correlate of the psychological and phenomenological changes that accompany psychiatric disturbances (Gloor et al. 1982; Persinger and Makarec 1987). The specific deterioration of neurons within these structures and the enlargement of the inferior horn of the lateral ventricles that surround these regions is well documented for patients who display significant thought disorders (Roberts and Bruton 1990). The insidious profile of this specific cell loss is consistent with the concept of frequent episodes of subclinical persistent paroxysmal activity that generates both the psychophysiological symptoms and the excitotoxic cell death.

Immediately relevant to this suggestion is the measurement of higher concentrations of dopamine within the (left) amygdala of brains from patients who have been diagnosed as schizophrenic (Swerdlow and Koob 1987). If melatonin suppression by increased geomagnetic activity disinhibits dopamine control, then enhancement of dopamine-mediated symptoms would be expected. Such symptoms would include unusual mannerisms and agitated motoric behaviors that could be considered equivalents of the oral dyskinesias and stereotyped movements displayed by our treated animals (Bureau and Persinger 1991), and alterations in thought and affect.

These changes are assumed to be mediated by corpus striatal and by limbic-cortical dopamine pathways, respectively (Swerdlow and Koob 1987). Both classes of behavior are diminished, although after different periods of treatment, by the antidopaminergic actions of neuroleptics such as chlorpromazine and haloperidol: mixed D1/D2 receptor and D2 receptor antagonists, respectively. Because the behavioral anomalies noted in the lithium/pilocarpine-seizured rats appear to be mediated by D1 dopamine receptors, amelioration of these symptoms should be more effective with specific D1 receptor blockers.

If these suggestions are correct, then the multiple endpoints that range from the enhanced cardiac death reported by Novikova et al. (1968), to the increased incidence of neuropsychiatric difficulties reported by Friedman et al. (1963), may be related to a single mechanism. One consequence of this mechanism is that singular sudden and intense geomagnetic storms, especially after a period of relative quiescence, would produce clear changes in the manner reported by Traute and Duell

(1935). On the other hand a period of frequent, intermittent geomagnetic perturbation may result in a wider statistical distribution of pathology, which would require wider temporal increments of analysis in order to be perceived; if this pattern were present, then removal of the "error variance" from weekly and monthly sources could also eliminate the geomagnetic effect.

In our study, significant increases in mortality, which we inferred as an index of the threshold for the geomagnetic effect, occurred when the daily aa values exceeded 20 nT (gamma); this is a frequent daily value during the active period of the 11 year solar cycle. If this threshold is correct, then the possibility must be considered that susceptible organisms, such as normal people who display limbic lability (Persinger and Makarec 1987), are very sensitive to geomagnetic changes.

There is accumulating evidence for this sensitivity. Decreased thresholds for convulsive seizures in human epileptics (Keshaven et al. 1981) and increased incidence of bereavement hallucinations (Persinger 1988) have occurred when the daily geomagnetic activity exceeded 20 nT and increased (from the day before) by an average of about 10 nT. Geomagnetic storms have exerted a dose-dependent effect upon homing behavior in pigeons; the estimated threshold for sensitivity to geomagnetic changes is between 10 and 30 nT (Semm 1988).

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